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# First episode psychosis and outcome findings from a swedish multi-centre study

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# *Till Frida*







## ABSTRACT

The Parachute Project was a Swedish multi-centre project that included 175 First Episode Psychosis patients who were followed over five years. The aim was to provide “need adapted care” with low medication and based on out-patient support in order to positively affect long-term outcome. One historical and one prospective “treatment-as-usual” group provided comparison follow-up data. The aim of this thesis is to describe outcome from various perspectives in FEP patients. Study I compared symptoms, functional outcome, care consumption and costs between the Parachute patients with a baseline schizophrenia syndrome and the comparison groups at three-year follow-up. Study II examined the relation of background variables to patients’ satisfaction with care (PSC) at 1-year follow up. Study III and IV explored the relation between background variables, baseline status gender and 5-year outcome. Study V examined the associations between perceived financial strain and qualitative and quantitative network to level of recovery after 5-years.

After three years the consumption of inpatient care had been significantly lower in the Parachute group than in the prospective comparison group. In spite of increased outpatient care in the Parachute patients’ group the total mean cost was about half of the cost in the Prospective comparison group. Symptoms and functional outcome were better compared to the Historical group but there were no differences compared to the Prospective group. At one year follow-up the Parachute Project patients showed a high satisfaction with the received care. Factors that were shown to be predictors of PSC were “educational level”, “social network”, “duration of untreated psychosis” (DUP) and “Global Assessment of Functioning (GAF) the year prior to onset” together with negative symptoms and lack of hope at admission. Twenty-nine percent of the variance in PSC was explained by these factors. At five year follow-up 85 patients (37 males, 48 females) showed a good outcome and 68 patients (44 males, 24 females) a poor outcome. The relative contribution of the baseline characteristics to the 5-year outcome was analyzed. The variables found to have unique contributions were: “GAF the year before first admission  $\leq 70$ ”, “highest educational level is compulsory school”, “GAF at first admission  $\leq 30$ ”, “male gender” and “contact with friends  $\leq 2-3$  times/month”. Furthermore, gender differences in the predictors were examined. “GAF the year before first admission  $\leq 70$ ” and “GAF at first admission  $\leq 30$ ” explained most of the variance of a poor 5-year outcome for males, whereas for females the corresponding items were “highest educational level is compulsory school”, “living with parents” and “contact with friends  $\leq 2-3$  times/month”. A predictive rating scale (PRS) was constructed from the results. After five years the Parachute Project patients answered a questionnaire from the PART study, a population-based study of mental ill health, which included questions about qualitative and quantitative network and experience of financial strain. The relation between these variables and outcome group (PART participants, recovered FEP patients and non-recovered FEP patients) was examined. The results showed that financial strain, quantitative social-network and qualitative social-network explained 16% of the variance in the outcome groups.

In summary, the results showed that it is possible to provide “need-adapted care” to persons suffering from psychosis, but further studies with a naturalistic design are needed to increase knowledge regarding what ingredients are effective and how various interventions interact. In addition it is important with early intervention to decrease the prodromal period and DUP. Outcome depended on various factors present before the first contact with psychiatry and those factors differ between the genders. Thus outcome measures have to be comprehensive and cover various aspect of a person’s life. It is not enough to measure outcome, i.e. only with symptom levels or diagnosis. More factors have to be examined and taken into account, such as gender, age, quality of life, amount of medication, social adversity and financial strain, both in treatment choices as well as in outcome measures.

Keywords: First Episode Psychosis; schizophrenia, long-term outcome; predictors; satisfaction with care;





## LIST OF PUBLICATIONS

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- II Mattsson, M., Lawoko, S., Cullberg, J., Olsson, U., Hansson, L., Forsell, Y. Background factors as determinants of satisfaction with care among first-episode psychosis patients. *Soc Psychiatry Psychiatr Epidemiol.* 2005 Sep;40(9):749-54.
  
- III Flyckt, L., Mattsson, M., Edman, G., Carlsson, R., Cullberg, J. Predicting 5-year outcome in first-episode psychosis: construction of a prognostic rating scale. *J Clin Psychiatry.* 2006 Jun;67(6):916-24
  
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## LIST OF ABBREVIATIONS

ACT	Assertive Community Treatment
BPRS	Brief Psychiatric Rating Scale
CBT	Cognitive Behavioural Therapy
CCT	Controlled Clinical Trial
CT	Computerized Tomography
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (fourth edition)
DUP	Duration of Untreated Psychosis
ECT	Electro Convulsive Therapy
EEG	Electro Encephalography
EPPIC	Early Psychosis Prevention and Intervention Centre
FEP	First Episode Psychosis
GAF	Global Assessment of Functioning
ICD	International Classification of Diseases
MRI	Magnetic Resonance Imaging
NOS	Not Otherwise Specified
PACE	Personal Assessment & Crisis Evaluation
PANSS	Positive and Negative Syndrome Scale
PART	In Swedish: Psykisk Hälsa, Arbete och Relationer
PORT	Patients Outcome Research Team
PRS	The Predictive Rating Scale
PSC	Patients' Satisfaction with Care
PSQ	Patient Satisfaction Questionnaire
QoL	Quality of Life
RCT	Randomized Controlled Trials
SCID	Structured Clinical Interview for DSM-IV
SPSS	Statistical Package for the Social Sciences
TIPS	In Norwegian: Tidlig Oppdagelse og behandling av Psykoser
WAIS-R	Wechsler Adult Intelligence Scale

N.B. The expression “Global Assessment of Functioning the year prior to onset “ in paper II is synonymous with the expression “Global Assessment of Functioning the year before first admission” in paper III and IV.



# INTRODUCTION

## HUMAN INSANITY IN HISTORICAL PERSPECTIVE

Through history human insanity has been viewed in many different ways. Signs of loss of reality have been interpreted and understood within the present cultural and historical context. A person who could “talk to the spirits” could be looked upon in a positive way as “having a gift from God” as well as in a negative way as “being possessed by the devil” (1). The kind of treatment meted out to the insane varied with time. Some were idealized and “declared as saints” but more commonly they were “outcasts”, punished and put together with criminals. It was first in the 19<sup>th</sup> century that asylums for only “madness” were established (1). The main objective was to hold those affected by insanity isolated from the rest of society. The treatment offered was sparse and could be, for example, hot and cold baths. Frustration over the lack of treatment alternatives led to psychiatrists and neurologists in the thirties starting to use various somatic methods such as insulin shocks, electro-convulsive therapy (ECT) and lobotomy (2). It was not until 1952 that specific pharmacological treatments, the first antipsychotic substance being chlorpromazine, targeting the psychotic symptoms were available. Even in the past few decades the views of psychosis and schizophrenia have swung backwards and forwards between that of regarding them as being purely genetic diseases to being a reaction to environmental stress, i.e. caused by a cold, rejecting and controlling mother, the so-called “schizophrenogenic mother”, meaning that schizophrenia was simply the child’s reaction to such a mother (3).

## WHERE DO WE STAND TODAY?

Nowadays large asylums and psychiatric hospitals are rare. Patients are to be integrated in society and as much as possible treated in outpatient care. There are different kinds of treatment available, pharmacological psychological and psychosocial. Although knowledge about causation, course and treatment has increased, there are still many unresolved questions. Attitudes and opinions based on prejudices and misconceptions are still very common. In a recently published paper (4) the authors showed that >50% of the lay public thought that persons suffering from psychosis and schizophrenia are more dangerous than the average person and almost all thought that schizophrenia is a non-treatable condition.

The following paragraphs will first give a brief description of the historical roots of the concept of psychosis and schizophrenia, the current knowledge about cause, prognosis, treatment and outcome in FEP. This will be followed by a presentation of five studies from the Parachute Project focusing on first episode psychosis patients and outcome.





# BACKGROUND

## THE CONCEPT OF PSYCHOSIS AND SCHIZOPHRENIA

Psychosis is defined as a mental disorder characterized by different degrees of loss of contact with reality and sometimes followed by deterioration of normal social functioning. The main and common symptom for all psychoses is the loss of reality testing due to misinterpretation of perception. Furthermore, symptoms such as hallucinations, disturbed behaviour and confusion can be present. Psychosis is the common term for all kinds of psychosis diagnosis; the most serious is labelled schizophrenia. Psychosis and schizophrenia are defined in phenomenological and psychological terms since no biological correlates are available. The diagnoses are therefore based on the presenting symptoms (5). The following paragraphs will give a brief historical perspective of how psychosis has been seen within the medical paradigm of the past century and how this is reflected in our current diagnostic systems.

### Nosology

Human nature has a need of structuring and categorizing the world. In the discipline of medicine, the systematic description and categorizing of diseases is called nosology. The 18<sup>th</sup> century is considered the dawn of scientific psychiatry because the first scientific views on madness were traced to nosologic outlines (1). The reigning paradigm of the past century has been the disease entity model leading to important distinctions between disease classes, especially in infectious disease but also for classification of psychosis such as the schizophrenia construct (6). Three important contributors to the development of the diagnostic concept are presented below.

### Emil Kraepelin (1856-1926)

Emil Kraepelin was a German psychiatrist and he has been regarded as the founder of modern scientific psychiatry. The efforts to demonstrate that psychoses had a definite morphological background failed and this encouraged him to try other methods. He correlated symptoms with course (7) and in 1896 produced the first detailed description of severe psychosis. He separated it from manic-depressive disorders that often had a better outcome and called it dementia praecox. Emil Kraepelin described dementia praecox as a chronic, deteriorating psychotic disorder characterized by rapid cognitive disintegration, usually beginning in the late teens or early adulthood. Except for this criteria he described Dementia Praecox as a heterogeneous disorder (5).

### Eugen Bleuler (1857-1939)

Eugen Bleuler was a Swiss psychiatrist most notable for his contributions to the understanding of mental illness. In 1911 he proposed the name schizophrenia instead of dementia praecox. In his view schizophrenia was held together by a fundamental dissociative pathology (6). Bleuler suggested that certain fundamental symptoms clearly indicated that schizophrenia has organic roots whereas the other symptoms were a psychological reaction to the fundamental symptoms (7). The diagnostic criteria for the fundamental symptoms of schizophrenia comprised Bleuler's "four A:s": *Associative disturbances* – affecting the patients ability to think logically, *Affective disturbances*: the patient's affect is incongruent with the current situation, *Ambivalence*: the patient can not make decisions and *Autism* –the interaction with physical and emotional environment. Symptoms as hallucinations and delusions were regarded as accessory i.e. not specific (5).





## Kurt Schneider (1887–1967)

Kurt Schneider was a German psychiatrist known largely for his writing on the diagnosis and understanding of schizophrenia. In the twenties he separated psychotic symptoms into first and second rank, in order to delineate symptoms that might mean a more serious progression. He regarded the first rank symptoms as being the most important in distinguishing between schizophrenia and non-schizophrenia psychosis. The first rank symptoms had bizarre contents such as: experiencing thoughts as being inserted by others, movements were controlled by others, hearing running commentaries from others and so on. The second rank symptoms were delusions, perplexity, as well as depressive and manic mood (5). However this separation has not proved valid in later prognostic studies (8).

## Positive and negative symptoms

A widespread categorization of psychotic symptoms is the distinction between positive and negative symptoms. This dichotomy has much in common with former descriptions of characteristic schizophrenic symptoms versus additional symptoms and was present in the thinking of the nosologic forefathers in the 20<sup>th</sup> century (some of them mentioned above). The terms negative and positive symptoms were first used by an English neurologist named John Hughlings Jackson in the 19<sup>th</sup> century to describe insanity. In the seventies Strauss et al. formulated the first explicit hypothesis that this distinction represented distinct pathophysiologies within schizophrenia (9). Soon after this Crow distinguished two syndromes of schizophrenia: Type I characterized by positive symptoms and Type II characterized by negative symptoms (10). He proposed that this distinction could be used to create a typology of schizophrenia (11). Many systems have been developed to define positive and negative symptoms, and symptoms that are considered positive and negative vary somewhat across these systems (9). One example of a frequently used scale is the Positive and Negative Syndrome Scale (PANSS) (12, 13). According to the PANSS the following symptoms are defined as positive: delusions, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution and hostility. The following symptoms are defined as negative: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking. The Brief Psychiatric Rating Scale (BPRS) is also often used in rating symptoms relevant for psychotic disorders. The concept of negative and positive symptoms has been used in connection with various theoretical conceptions; ranging from the purely descriptive to notions of aetiology or pathophysiology (10).

## SOME CONSEQUENCES OF THE ADOPTED CONCEPT

As we can see, the efforts to delimit psychotic disorders have often been based on the assumption of prognosis and in particular poor prognosis because of the lack of biological markers. Thus the diagnosis has the inherent expectancy of a poor outcome. Investigations in psychiatry have begun with the establishment of class membership; criteria for, e.g. schizophrenia, have to be fulfilled. This kind of classification of a rather heterogeneous group causes problems and makes it difficult to interpret research results. Even with a narrow definition of schizophrenia 10-30 % of the patients will fully recover with no signs of residual symptoms. Another problem is that the impact of having a negative expectancy might per se increase the risk of poor outcome (14).

The currently used diagnostic systems have their roots in the diagnostic history described above (5). They are more or less based on the expectancy of poor outcome despite the fact that outcome varies markedly. The limitations of the current diagnostic tools (which will be described further below) have been the subject of much debate. Much effort has been made to manualize the diagnostic assessment so that different assessors will come to the same results: However, the high reliability of a modern diagnostic tools does not necessarily mean validity(15).





The different ways that have been used to categorize psychosis over the past century and the heterogeneity within each category are reflected in the various and sometimes conflicting results in follow-up studies of psychosis. For obvious reasons (great efforts are made with those who not will recover promptly) most studies have been performed on long-term functional psychosis but the inclusion criteria and the labelling of those included in the studies have varied. Thus the following brief review of the current “state of the art” regarding psychosis mostly includes long-term functional psychosis, often labelled schizophrenia. The exceptions are studies of first episode psychosis, which also includes brief psychotic disorders. It is impossible to make a valid distinction between the different concepts that have been used by different authors in categorizing psychosis. Therefore, when results from other studies are presented in this thesis the terms psychosis and schizophrenia can sometimes be considered interchangeable.

## DIAGNOSTIC SYSTEMS

Nowadays there are two main diagnostic systems in use. The International Classification of Diseases-10 (ICD-10), which covers all diseases and was endorsed by the Forty-third World Health Assembly in May 1990, came into use in WHO Member States as from 1994. Since 1948 WHO has the responsibility for the ICD and its creation (16). The diagnostic system recommended in psychiatric research is the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) which only covers mental disorders (17). Of all persons who receive their first episode psychosis (FEP) 30 to 50 percent will fulfil the criteria for a schizophrenia diagnosis.

A diagnosis of *schizophrenia* according to the DSM-IV system is defined as follows:

- **Criterion A.** At least two of the following characteristic symptoms have to be present: delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behaviour, negative symptoms, i.e., affective flattening, alogia, or avolition. Only one of these symptoms is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the persons behaviour or thoughts, or two or more voices conversing with each other.
- **Criterion B.** Social and/or occupational dysfunction.
- **Criterion C.** Continuous signs of the disturbance have to persist for at least 6 months and this period must include the characteristic symptoms for at least one month. If only the characteristic symptoms (criterion A) are present and the duration are less then 6 months the patient will get a schizophreniform disorder diagnosis.
- **Criterion D.** Schizoaffective and mood disorder exclusion.
- **Criterion E.** Substance/general medical condition exclusion.
- **Criterion F.** Relationship to a Pervasive Developmental Disorder.

Other psychotic disorders diagnoses are defined as follows:

- *Schizoaffective disorder* with characteristic symptoms of schizophrenia (criterion A) interrupted by either a major depressive period, a manic period or a mixed episode.
- *Delusion disorder* includes non-bizarre delusions (i.e. involving situations that can occur in real life such as being followed). Criterion A for schizophrenia is not met and the functioning and behaviours is not markedly affected.





- *Brief psychotic disorder* - the following symptoms should have been present for at least one day but less than one month: hallucinations, disorganized speech (e.g. frequent derailment or incoherence), grossly disorganized or catatonic behavior.
- *Mood disorders* with psychotic symptoms (not criterion A), congruent or incongruent to the depressed or elevated mood.
- A diagnosis of “*Psychotic disorder not otherwise specified*” will be set if there are lack of adequate information to set a specific diagnosis of a psychotic disorder.

Psychotic symptoms can also be due to physical disturbances, poisoning, drug abuse and brain damages.

The DSM-IV system also includes judgement of the individual’s overall level of functioning using the Global Assessment of Functioning (GAF) scale. The scale rates from 1 to 100 and includes both symptoms and functioning. A person with a superior functioning in a wide range of activities, whose life’s problems never seem to get out of hand and who does not have any symptoms will have a GAF score of >90. A person with mild symptoms or some difficulty in social, occupational or school functioning but generally functioning quite well will have a GAF score of >60. A person affected by psychotic symptoms will have a GAF score of ≤40.

## EPIDEMIOLOGY

Mental health disorders are an increasing problem affecting a significant part of the population. Studies suggest that up to 27% experience a mental health problem (18) and almost everyone knows an affected person. Mental problems reduce the quality of life of both the affected persons and their families. The European Union states that mental health problems are currently the leading cause of disability and the most common disorders are anxiety and depression. In Europe, depression is present in 4.5% of the general population every year (prevalence 45/1000<sup>1</sup>) (19). Depressive emotions and anxiety are conditions that everyone of us have experienced to some extent thus facilitating the empathy and understanding for those who suffer from these kind of psychiatric problems. More serious psychiatric conditions such as psychosis and schizophrenia have a lower incidence<sup>2</sup>. This also varies geographically due to substantial variations in gender, urbanicity and migrant status. It should be noted that most studies of incidence and prevalence concern schizophrenia although the definition of schizophrenia can vary. In a systematic review of the incidence of schizophrenia by McGrath et al., including data from 33 countries, discrete core data from 55 studies showed an asymmetric distribution and had a median value of 15.2 (7.7-43) /100.000 persons per year (20). A systematic review of the prevalence of schizophrenia including 188 studies drawn from 46 countries showed a median value of point prevalence of 0.5 % (4.6/1000), which can serve as an estimate of one-year prevalence and be compared with the numbers regarding depression presented above (21). The onset of schizophrenia is generally at a young age, most of the males are affected in the late teens and most of the females in their late twenties. Despite the fact that the incidence and prevalence in psychosis and schizophrenia are low a substantial share of the psychiatric resources is consumed by this group (22).

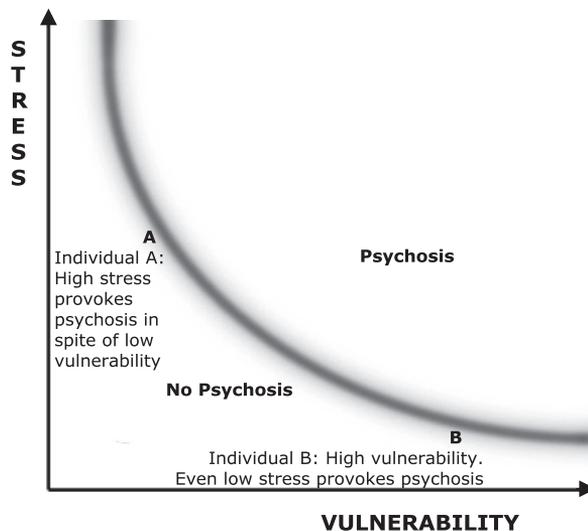
1 The number of all cases at a certain time  
 2 The number of new cases at a given period





## AETIOLOGY

Although there is not one specific cause there are a number of known factors that increase the risk of developing psychosis and schizophrenia. As in many other disorders genetic and environmental factors interact in the development of schizophrenia (23-25). The genetic background to psychosis and schizophrenia is complex and there is still a lack of knowledge about the process of the development. However, prevention involving targeting genes is a complicated issue and hard to practice while maintaining a humanistic perspective in a democratic society (26). The environmental factors that have been shown to be related to psychosis and schizophrenia are: obstetric complications, season of birth, drug abuse, migration and ethnicity, urbanicity (25), social adversity (24) and trauma (27) in childhood. Some of these factors can be targeted in primary prevention (see paragraph prevention page 16 about primary prevention). The interaction between the individual's vulnerability and stress from the environment is summarized in the Stress-vulnerability model (28) which proposes that if the individual has a high degree of vulnerability it demands less exposure to stressors for the individuals to express ill health and vice versa.



## Research design

As mentioned before, former studies of psychosis have often used different criteria for the diagnosis of schizophrenia. Some studies have used wide criteria and have included almost all psychosis not due to substance abuse and medical conditions in a schizophrenia diagnosis. Other studies have used narrow criteria for a schizophrenia diagnosis. Thus the possibility of comparing results in different studies is limited.

The gold standard of efficacy studies today is randomized controlled trials (RCT) (29). The participants are randomized to either effective or placebo or no intervention. The researchers can take into account, and have control of, most of the aspects that can confound or mediate the results. The results from these studies can be generalized and repeated under standardized conditions. However, sometimes it is not possible or appropriate to perform an RCT. A quasi-experimental designed study might be an alternative. In a controlled clinical trial (CCT) patients who receive a particular treatment are compared with another group/ other groups who are receiving another or no treatment. Observational studies follow a group/groups of persons over time and in contrast to RCT observational studies allow the assessment of the effectiveness of an intervention in real life health-care settings. In this design the control of possible confounders are limited but the face





validity<sup>3</sup> is higher (29). The results are generated in real life and can therefore be applicable to real life. In many studies these designs are mixed.

## COURSE AND OUTCOME

Historically outcome in schizophrenia has been looked upon pessimistically. Emil Kraepelin, believed that dementia praecox (later called schizophrenia by Manfred Bleuler) had a deteriorating course in which mental function continuously declined (30). Later studies have changed this to a more optimistic view even if studies have shown varied results (31-33). For example, the Vermont State Hospital Follow-up Study showed that after twenty years 60 % of the patients diagnosed with schizophrenia scored >60<sup>4</sup> on GAF and did not differ compared to other psychiatric patients. The Iowa 500 follow-up study yielded different results: the schizophrenic patients had a poorer outcome compared to other patients. Despite this, 30 % of the schizophrenic patients were married and 20% emerged from the study free from symptoms (31). An European study by Shepherd et al. (8) rated social impairment and after five years 45 % of the schizophrenia patients only showed minimal impairment, 43% mild to moderate and 12% severe impairment. A systematic review of longitudinal outcome studies of first-episode psychosis report that good outcome was reported for 42% of the population, an intermediate outcome for 35 % and a poor outcome for 27% (32). Most outcome studies show that schizophrenia patients have a poorer outcome than patients with other types of psychiatric disorders (31). However, the inclusion criteria for schizophrenia differ in several of these studies, giving sometimes broader or narrower borders, and differences in results regarding outcome can be due to this. Additionally, the differences can be due to lack of uniform assessment methods, varying statistical approaches, different stages in the process of the disease and different treatment regimes (31). Differences can also be due to true variance and an indicator of heterogeneity in the diagnostic categories. The DSM-IV system is based on the premise that schizophrenia is a discrete illness entity and the role of culture, ethnicity and life course is not taken into account (15). Models using both categorical and dimensional representations of psychosis might be better discriminators of course and outcome than either model independently (34).

### Outcome measures

There is no commonly used standard measure of long-term outcome in psychosis and schizophrenia. A wide variety of outcome measures are used, such as clinical symptoms, hospitalization, effect of medication, social-, occupational functioning, quality of life, marriage, social support symptom outcome, functional outcome, and mortality (35). Andreasen et al. (36) have stressed the need of consensus in used measurements to enable studies to be comparable and to enable evaluation in daily practice. They have proposed a way of measuring symptom remission. However, symptom scores cannot give comprehensive information about the patient's situation. Outcome has multiple facets, which vary in importance between patients. Symptom rating scales play an important role in overall appraisal of outcome but they have to be complemented by measures of personal, social and cognitive functioning (37) together with the patient's subjective view (38). The distinction between remission (very small, or no sign of the disease, only affecting life marginally) and recovery (not having the disease, being healthy) is another area where common guidelines need to be developed.

## FACTORS RELATED TO OUTCOME

Factors that have been shown to be related to poor outcome are: male gender (39-46), poor pre-morbid functioning and long Duration of Untreated Psychosis (DUP) (41, 44-59), a baseline diagnosis of schizophrenia spectrum disorder (41, 45, 60), low education level (45, 46, 61), lack

<sup>3</sup> The subjective impression of a test's meaningfulness in a certain context.

<sup>4</sup> GAF score > 60 indicates that the patients have mental problems to an extent that does not demand psychiatric care.





of social support (62-64), more negative symptoms<sup>5</sup> (48, 65-70), cognitive dysfunction (71-73), abnormal electro encephalographic (EEG) findings (74), a family history of psychosis (42, 60), lateral ventricular enlargement (75), non-adherence to treatment (e.g. medication) (59, 76) and poor working alliance (77). It is not possible to affect all of these factors but efforts have been made to, e.g. intervene early by identifying the patient during the prodromal<sup>6</sup> period and to shorten DUP period with positive results (78). More about prevention and treatment is to be found in paragraphs prevention page 16, treatment page 17 and integratet treatment page 18.

## **GENDER AND PSYCHOSIS**

Male and female patients with psychosis differ in many ways. Males have an earlier onset, a lower pre-morbid level of functioning, more negative and less affective symptoms and a higher risk of poor outcome compared to females (39, 43, 79-82). In spite of this, treatment programmes are rarely gender-specific and usually provide the same care for both genders.

## **EXPERIENCING PSYCHOSIS**

The experience of suffering from a psychosis, or having a relative or friend suffering from a psychosis, can be traumatic in various ways. The onset can be acute with florid symptoms from one day to another but more often the onset has had an insidious course of events. The patient can start to experience problems with sleep, increased anxiety, brooding, depression and feelings of unreality (83). The immediate surroundings on the other hand can start to register change or odd behaviour. The experience is new for all who are involved for the first time and the psychotic symptoms can be frightening for both the patients and their social network. Most people have pre-conceptions of psychiatric illnesses, mostly negative. When someone has their first onset of psychosis the experience is merged with the pre-conception that the affected person and the surroundings are carrying. These pre-conceptions can be that psychiatric treatment is more harmful than helpful and that the general practitioner is more reliable than the psychiatrist thus affecting the pattern of help seeking (84, 85). Pre-conceptions such as internalized cultural values will also affect the patient's judgment of his own value and this might lead to social anxiety and shame (86). The loss of the known reality, the unknown milieu in the treatment setting that the patient will encounter and the stigma that pre-conceptions and prejudice can create are what patients have to cope with.

## **PREVENTION**

Prevention can be divided in:

- Primary prevention – to forestall the occurrence of an illness
- Secondary prevention – to shorten the duration of illness and ensure treatment effective
- Tertiary prevention – to prevent further manifestation of the illness, rehabilitation (83).

### **Primary intervention**

As mentioned before, onset of schizophrenia is related to a number of unspecific risk factors, both genetic and environmental and it is currently the environmental risk factors that can be targeted in primary intervention. By giving optimal antenatal, perinatal and postnatal care and avoiding obstetric complications, by fighting social adversity and drug abuse and by supporting young people with signs of social and psychological difficulties we might prevent some cases from developing into psychosis and schizophrenia.

5 Withdrawal, isolation, lack of interest in surroundings

6 Unspecific symptoms preceding the psychotic symptoms





## Secondary intervention

Reducing DUP is of importance in efforts to support recovery. Early intervention projects aiming to start treatment as soon as possible and to deliver psychiatric services close to the patient's needs have shown promising results (44, 45, 78, 87-91) To influence the risk of developing chronic deficits much effort has been made in affecting the course of the psychosis by developing methods and treatment that affect outcome. The treatment given should follow evidence-based recommendations of integrated treatment, see paragraph integrated treatment page 18.

## Tertiary intervention

Despite efforts to reduce symptoms and avoid the development of permanent decline in function some persons will not recover to a full extent. In those cases it is important to give support and treatment in a way that does not provide iatrogenous<sup>7</sup> effects. Side effects of medication and hospitalization in closed psychiatric wards are examples of this. In addition, shame and stigma (86) can be a further burden as is constant financial strain.

## TREATMENT

The treatment in psychosis and schizophrenia can be divided into:

- Pharmacological treatment
- Psychological treatment
- Psychosocial interventions

They are usually combined.

## Pharmacological treatment

The first antipsychotic medication, chlorpromazine, was introduced in 1952 and meant a revolution in the treatment of psychosis and schizophrenia. After the first optimistic period it became clear that not every patient was helped by the medication, e.g. many of the negative symptoms did not respond to antipsychotic treatment. Another complication is that antipsychotic medication has side effects that can prevent patients from using it. The first generation antipsychotic medication, also called typical, can give extrapyramidal side effects such as, akathisia, paresthesia, rigidity and hormonal disturbances. Newer antipsychotic medication does not have these motorical side effects although some can result in metabolic disturbances, such as weight gain and diabetes (92, 93). Side effects are partly dose dependent and in current guidelines the lowest possible dose is recommended.

## Psychological treatment

Psychological treatment has varied according to time and fashion. From the sixties to recently (in Sweden) the psychological treatment was mainly based on dynamic methods from the psychoanalytical school. A person's symptoms were interpreted within the theory of the inner world and its representations and the way to recovery was to increase the person's insight into the unconsciousness patterns that experience has created and that rules our lives. A recent review by the Cochrane Collaboration states that there is little evidence of any positive effect of a psychodynamic approach for people with schizophrenia and severe mental illness. However, there is rather a lack of evidence than a presence of evidence that demonstrates a lack of positive effect (94). Over the past decades Cognitive Behavior Therapy (CBT) has attracted more interest and has become more common in the care of severe mental illnesses such as psychosis and schizophrenia. CBT focuses mainly on how to change the patients' behaviour and to some extent on the patient's pattern of thinking. A review from the Cochrane Collaboration (95) found that there is some evidence that

7 Iatrogenous effects are illness caused by the care/treatment.





CBT can reduce positive symptoms but there are few randomized controlled studies and the sample sizes are often small. Supported therapy defined as interventions with the aim of maintaining current functioning or to assist with a person's pre-existing abilities has not shown positive results when reviewed by the Cochrane Collaboration (96). Family therapeutic interventions have shown promising results in reducing burdens within the family and general social impairment, improving compliance with medication, decreasing relapse risk and re-hospitalisation and increasing Quality of Life (QoL) (97). Family intervention can include psycho-education in order to positively affect attitudes to, and understanding of, psychiatric illness. Psycho-education has also been shown to further improve psychosocial functioning and to reduce relapse and re-admission rates in people with schizophrenia (98).

### Psychosocial interventions

The psychosocial strategies aim to support the individual, according to his/her capabilities, in becoming a better functioning member of society and in living as good a life as possible. The interventions include the client's natural network such as family and friends. The intervention can be support in daily life and sheltered employment. Psychosocial interventions are crucial components in all treatment models in psychosis and schizophrenia.

## INTEGRATED TREATMENT

The view that the patient is a member of society with whom the psychiatric care services has to cooperate and the importance of considering the patient's views on the care (24) have gained ground over the past decades although the outcome of FEP in the present psychiatric care system is still unsatisfactory. A Swedish study showed that 74% of the patients suffering from schizophrenia and 47% of persons suffering from other psychosis were on disability pension or on long-term sick leave after five years (99). "Treatment-as-usual" with lack of continuity in care, large inpatient wards where patients with different problems and ages are mixed, and standardized high doses of antipsychotic treatment leading to troublesome side-effects have been considered counterproductive in meeting the needs of FEP patients. It is of importance to meet the clinical need early, comprehensively and with the best possible available combination of psychosocial and biomedical interventions (100). Multi-elements programmes specially designed for the needs of young individuals when experiencing their first-episode psychosis have shown promising results. Integrated treatment can be based on Assertive Community Treatment (ACT). ACT is a team-based approach, characteristically a multi-disciplinary team, including social workers, nurses and psychiatrists, caring exclusively for a defined group of patients. ACT is designed to provide comprehensive, community-based psychiatric treatment, rehabilitation, and support. Services are preferably provided within community settings, such as the patient's own home and neighbourhood, local restaurants, parks and nearby stores. The service should be highly individualized and treatment plans developed in cooperation with the patient. The patients are encouraged to participate in community activities and to become members of organizations of their choice in order to prevent social isolation. The interventions include the client's natural support systems (family, significant others) in the treatment. The team follows the patient over time and in different treatment settings such as inpatient and outpatient care. A recent report from the Cochrane Library found that ACT reduces the use of inpatient care, improves some aspects of outcome (inpatient care, employment, patient satisfaction) and maintains the contact over time in patients with severe mental disorder (101). In a Swedish study of schizophrenic patients Malm et al. found that an integrated care model including social-network resource groups with procedures of shared decision making and structured communication and problem solving training improved two-year outcome in social function and consumer satisfaction (102).





## Sources of inspiration

The Parachute Project has been inspired by several projects in the field of integrated treatment.

### *The need-adapted model*

The most important example is the need-adapted model in Finland developed in the middle of the eighties. The model was based on the following principles:

- Therapeutic activities should be based on a psychotherapeutic attitude and governed by the needs of the patients and the family
- The different therapeutic activities should support and not impair each other
- The process in treatment should be continuously evaluated by assessment of the course and outcome of the treatment (103).

### *Soteria Bern*

Another source of inspiration was the “Soteria”- concept. “Soteria” stands for an alternative low-drug milieu-therapeutic approach to acute schizophrenia that was first implemented by Mosher and Menn in San Francisco (104). The Soteria Bern project started in the middle of the eighties.

The model of Soteria Bern consisted of the following eight principles:

- Acute psychotic patients should be treated in small, open, friendly and family-like houses for 6-8 patients with a garden, in the midst of the community and continuously staffed by two nurses,
- During the most acute state the patient is never left alone; personal and conceptual continuity is prioritised (staff work 48-hour shifts)
- Half of the staff should have a psychiatric profession and the other half different professional qualifications, the team should be half male and half female,
- Close collaboration with the patient’s family and network,
- Continuous provision of clear, comprehensive and convergent information about the illness, evolutionary risks, the treatment methods used and relapse prevention,
- Systematic formulation of concrete therapeutic aims concerning the future, housing and employment,
- Low dose antipsychotic medication used selectively,
- Educating patient and family members in post care and relapse prevention techniques.

In Sweden the Soteria Nacka model with need-adapted treatment has shown promising results (105).

## Early intervention projects

Examples of other important projects concurrent with the Parachute Project are the Early Psychosis Prevention and Intervention Centre (EPPIC) project in Australia and the Early Treatment and Identification of Psychosis Project (TIPS), in Norway and Denmark, both aiming to reduce DUP and provide intensive phase-specific treatment in order to improve outcome in FEP.

The EPPIC is a comprehensive early intervention treatment programme that includes extensive assessments, outpatient case management, CBT, low-dose antipsychotic therapy, specialized inpatient unit, a mobile crises intervention ACT-team, group programmes, family support groups





and specialized treatment of enduring psychotic symptoms (90, 91). EPPIC works together with the Personal Assessment & Crisis Evaluation (PACE) clinic which focuses on young people aged 14-30 at risk of developing psychosis (106).

The TIPS project is a prospective clinical trial to test whether the timing of treatment in FEP patients can improve course and outcome (89). The TIPS services deliver optimal treatment according to the Patients Outcome Research Team (PORT) recommendations combining medications with psychosocial treatments, including psychological interventions, family interventions, supported employment, assertive community treatment, and skills training (107) in four healthcare sectors. Two of these are situated in Rogaland County in Norway and have developed a system for early detection including a comprehensive education and detection system designed to enhance knowledge about early signs of psychosis among the general public schools and professionals. The other two sectors situated in Ullevål in Norway and Roskilde in Denmark rely on existing referral system for psychosis and are used as comparisons (88).

Two clinical research projects have used RCT design to compare integrated treatment in FEP to standard treatment. In the OPUS study in Denmark three teams two in Copenhagen and one in Aarhus offered an enriched ACT model for the FEP patients over a period of two years. The programme consisted of ACT, psycho-educational multifamily treatment, social skills training and antipsychotic medication. The OPUS study found that the integrated treatment reduced the proportion of patients with poor clinical and social outcome after one year (108).

The Lambeth Early Onset (LEO) Team was a multidisciplinary community team in England established on the principles of assertive outreach, providing an extended hours service by including weekends and public holidays. Evidence based interventions adapted to the needs of people with early psychosis included low dose atypical antipsychotic regimens and cognitive behaviour therapy. The 18 month follow-up showed that the LEO patients had lower rates of readmissions and drop-out than the patients who received standard treatment (109).

## **THE PARACHUTE PROJECT MODEL**

The Parachute Project was a Swedish multi-centre project that started in January 1<sup>st</sup> 1996 (110). The Parachute Project represented an effort to provide comprehensive care for FEP patients. Nineteen clinics participated, seven in the Stockholm area and the others spread out over the country. The catchment area covered about 1.5 million inhabitants representing one-sixth of Sweden's population. The participating clinics had to guarantee clinical and research follow-ups over a 5-year period. Further, the clinics were expected to adhere as closely as possible to the following six clinical principles, which were rather close to the Finnish "need-adapted" model. The principles of the Parachute model were:

- Early intervention: first meeting with the patient within 24 hrs,
- Initial structuring crisis intervention,
- Immediate and recurrent family/network meeting,
- Continuity and accessibility to the multidisciplinary team for five years,
- Lowest effective doses of antipsychotic medication – if possible avoiding antipsychotic medication during the first week,
- Overnight care in low stimulus homelike small-scale crisis homes.

More data regarding the Parachute Project are presented in the Method section.





## AIM OF THE THESIS

The aim of the thesis is to describe outcome from various perspectives in FEP patients. The following areas are focused upon:

- A comparison between outcomes in FEP patients receiving comprehensive treatment according to the Parachute model versus “treatment-as-usual”
- Pre-onset predictors of patients’ satisfaction with care after one year in treatment
- Predictors of five-year global outcome and the development of a predictive rating scale
- Gender specific issues regarding predictors of outcome
- Socio-economic issues in five-year outcome



# MATERIAL AND METHOD

## THE STUDY GROUP

Data from the Parachute Project have been used in all the studies (110). The Parachute Project was a multi-centre study including patients living in the catchment area, seeking psychiatric help for the first time for psychotic symptoms, age 18-45 years with no serious somatic illness, dominating substance abuse or neurological disorder. Inclusion diagnoses according to the Diagnostic Statistical Manual (DSM-IV) (17) were: Schizophrenia, Schizophreniform psychosis, Schizo-affective psychosis, Delusional disorder, Brief Psychosis and Psychotic Disorder Not Otherwise Specified (NOS). Affective disorder with non-congruent psychosis was also included. The clinics were invited to take part in a combined clinical and research project focusing on all first episode psychosis patients. Recruitment of patients started after a series of meetings with representatives from the participating clinics. These meetings included appointment of local coordinators, selection of research instruments, video and role-play training in diagnostic assessments and symptom ratings. Study groups were formed for the neuropsychological and the Rorschach tests. Continued consensus training was provided during biannual conferences with 40–50 participants from the participating clinics. The conferences have also been used to give feedback and to discuss collected data. The project coordinator has run the central database set up in Stockholm. The local coordinators, usually psychologists, were responsible for the collection of follow-up ratings, interviews, tests, and for the communication with the central database. The degree of organizational compliance to the treatment principles was assessed through recurrent telephone interviews with the local coordinators. The collection of cases started 1 January 1996 and ended 31 December 1997 (24 months). Two clinics were unable to collect data and were excluded from the study during the first year, which resulted in 17 participating clinics. During the two inclusion years 253 patients fulfilled the criteria and 175 were included in the project.

## MEASUREMENTS

A summary of the assessments used in each follow-up period can be seen in Table 1.

Table 1. Research schedule in the Parachute Project

1 <sup>st</sup> week	1 Month	3 Months	6 Months	1 Year	3 Year	5 Year
DSM-IV				DSM-IV	DSM-IV	DSM-IV
Checklist of treatment interventions						
BPRS						
GAF						
Strauss-Carpenter				Strauss-Carpenter	Strauss-Carpenter	Strauss-Carpenter
Socialstatus	Life and family history			Socialstatus	Socialstatus	Socialstatus
	Rorschach	Rorschach		Rorschach	Rorschach	Rorschach
	WAIS-RNI				WAIS-RNI	WAIS-RNI
Birth record*	MR/CT*, EEG*					
				Family/patient satisfaction	Family/patient satisfaction	Family/patient satisfaction
				Test's 21	Test's 21	Test's 21
					HoNOS	HoNOS
						PART-questionnaire
						Comprehensive outcome

\* only schizophrenia syndrome

During the first week all patients with the potential of being included were diagnosed with a Structured Clinical Interview for DSM-IV (SCID) interview (Axis 1) (17) – usually performed by the



responsible psychiatrists. Those patients who agreed to participate in the study were re-diagnosed at 12, 36 and 60 months after baseline. The baseline diagnosis was revised at the 12-month assessment. Checklists regarding pharmacological, psychological, and organizational aspects of treatment were completed at each follow-up occasion. Antipsychotic medication was registered for seven periods (1<sup>st</sup> and 4<sup>th</sup> week, as well as the last week of the 3<sup>rd</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 36<sup>th</sup> and 60<sup>th</sup> month), and later calculated according to total amount of prescribed antipsychotic medication, transformed to haloperidol equivalents per day during the actual period. Information about individual and family psychiatric history and the patient's social contacts, working and financial situation was collected via interviews during the first month. The BPRS 24 item-version (111) was used to assess the type and degree of symptoms. Scores for positive and negative psychosis symptoms were later constructed. GAF-values (112) were used to measure symptom severity in combination with social functioning level. In addition, patient's and relatives' satisfaction with care were measured (110) (see paragraph 3.5). In 120 of the patients it was possible to collect neuropsychological assessment data, using the Swedish version of the Wechsler Adult Intelligence Scale (WAIS-R) (113-115). The first neuropsychological assessment was carried out within the first three months following admission in the vast majority of the patients (71). The psychological examinations also included the personality-focused Rorschach test, self-ratings of the patients' own relation to people in their surroundings as well as the relation to their own life situation. Computerized tomography (CT) alternatively magnetic resonance imaging (MR), as well as electroencephalogram (EEG) were carried out on patients with schizophrenia syndrome and their childbirth records were requisitioned. A cost-benefit analysis was performed independently at the Department of National Economy, University of Växjö. Data were also obtained from collateral sources such as relatives and network.

### The Patient Satisfaction Questionnaire

A specially constructed scale regarding degree of "satisfaction with care" was given to the patients at the 12-month follow up, to be completed separately and sent directly to the database in stamped, addressed envelopes. The Patient Satisfaction Questionnaire (PSQ) consisted of 13 items, five items regarding the first week in contact with psychiatry and the rest of the items regarding the first year of treatment. The items in the PSQ were based on the aims formulated for the Parachute Project (110, 116). Study II was based on analyses of the PSQ and the scale is presented fully there.

### The PART study

The PART study is a longitudinal population-based study of risk and protective factors for mental ill health in progress in Stockholm County, Sweden. For a detailed description see Hällström et al. (117). In the years 1998 to 2000 a questionnaire was sent to 19,742 persons, aged 20-64 years, randomly selected from the Stockholm city council register. The questionnaire included risk and protective factors for mental illness as well as psychiatric symptom scales. The participation rate was 53% (10,441 persons). An extensive non-participation analysis was conducted using available official registers. Participation was found to be related to female gender, higher age, higher income and education, being born in the Nordic countries, and having no psychiatric diagnosis in the hospital discharge register as well as in the early retirement register. The odds ratios for the associations between age, gender, income, country of origin, sick leave and in-patient hospital care due to psychiatric diagnosis were similar among participants and non-participants. All participants from the first wave received a new almost similar questionnaire three years after (year 2000-2002) they answered the first. The participation rate at the second wave was 79 % (n= 8 622). The non-participants were younger, and more often males. During the sixth year (2001) of the Parachute Project the PART questionnaire was sent to 133 of the remaining Parachute patients





## Outcome measure

In Study III, IV and V a comprehensive outcome measure was used based on assessments during the 5<sup>th</sup> year after first admission. It was possible to obtain this measure from 153 patients. A poor outcome was defined as “in need of continuous antipsychotic medication and support from professionals in everyday matters”. Such patients cannot work or study independently, require supported/sheltered jobs, or lead an inactive life. The GAF score had to have been <60 for at least the past 6 months. A good outcome was defined as “living a normal life” with or without antipsychotic medication and with no need for daily support from professionals”. The GAF score had to have been stable  $\geq 60$  for at least six months and they had to have worked or studied independently at least half time.

## COMPARISON GROUPS

As the participating clinics were too small to provide different treatment models, it was not possible to randomize the patients into experimental and control groups and due to this external groups were included.

### Historical comparison group

A historical comparison group was assembled at three of the project’s Stockholm clinics where so-called standard psychosis treatment had been provided, i.e. treatment primarily focused on pharmacological and supportive treatment. The study included all FEP patients during the years 1991–1992 (five years before the Parachute Project) who were followed-up over a period of five years. The inclusion criteria were the same as those used in the Parachute Project (except that affective psychosis was not included). Two specialist psychiatrists established the diagnoses using a consensus procedure. The GAF-assessments, along with estimates of care consumption, prescription of medicine, and sick-list data were based on hospital records as well as available databases.

### Prospective comparison group

A prospective comparison group was provided by the psychiatric clinic at Uppsala University hospital. The treatment in the comparison groups was considered as “treatment-as-usual”. As in the Parachute Project, a low dose of antipsychotic treatment was routinely recommended including efforts to avoid treatment with anti-psychotics during the first week. The main difference compared to the Parachute Project was that all first episode patients were evaluated and treated as inpatients on a psychiatric research ward together with young and old long-term patients; no specific psychological or family treatment was offered to first episode patients. The aim of the Prospective group has been to include every first episode psychosis patient during the years 1995, 1996 and 1997 with the same inclusion and exclusion criteria as in the Parachute Project. As the Uppsala study had already started when co-operation with the Parachute Project was decided upon (the Uppsala study had from the beginning the intention to examine outcome among FEP patients in the region) some of the Uppsala methods are slightly different. The data were sent to the Parachute database, and controlled and treated in the same way as were the Parachute Project data.

## PARTICIPANTS AND NON-PARTICIPANTS

### The Parachute Project

Out of the total 253 FEP patients that fulfilled the inclusion criteria in the Parachute Project 175 were included in the project. Thirty-seven did not wish to participate because of reluctance to appear in a case register. The remaining 41 could not be included as they moved from the area early in the treatment process, had language difficulties, or otherwise due to practical circumstances or unknown



reasons. Patients that moved to another area after six months of treatment were followed-up unless they refused to participate.

The non-participants were significantly older (32.1 years) than the participants (28.7 years) and there was a trend that non-schizophrenic patients (baseline) did not participate, especially those with delusional syndrome and brief psychosis. A summary of the participants at each follow-up is shown in Table 2.

Table 2. Number of participants in the study

Follow up	N	Drop out/Non participants
Total group	253	FEP patients 1996-1997 at 17 clinics
Baseline	175	FEP patients included in the Parachute Project
1 Year	164	Non participation rate 6% (N=11)
3 Year	149	Non participation rate 9% (N=15)
5 Year	135	Non participation rate 8% (N=14)

### The historical comparison group

In the historical comparison group all patients (n=71) were followed-up through patient records, databases and, in some cases, by questioning the caregivers.

### The prospective comparison group

In the prospective comparison group 13 of 64 (20%) patients did not want to participate in the investigation or could not be contacted for assessments at the 12-month follow-up. They did not differ significantly from the rest of the Prospective group regarding age, gender and distribution of schizophrenia/non-schizophrenia diagnoses.

## STATISTICAL METHODS

The analyses were made with the SPSS statistical packages for Windows version 12-14.

In all studies the socio-demographic variables were summarized using standard descriptive statistics such as mean, median, standard deviation and frequency. Differences in categorical data were analysed with chi-square, or Fisher's Exact Probability Test if the expected cell frequencies were less than 5. Differences in continuous data were analysed with t-test if the distribution was normal or Mann-Witney's test if the distribution was skewed.

*The following analyses were also used:*

In Study II a stepwise linear regression analyses was performed to examine background and baseline determinants for patients' satisfaction with care one year after first admission.

In Study III the unique contributions of the predictors to outcome were examined with stepwise forward logistic regression analyses.

In Study IV the relationships between the dichotomized variables were expressed as Pearson's product moment correlation coefficients. Differences between groups in the correlation coefficients were checked by comparisons of correlation coefficients obtained by means of Fisher's z transformation. The unique contributions of the predictors to outcome were examined with stepwise forward logistic regression analyses.

In Study V the associations between the qualitative- quantitative network, financial strain and outcome group were examined with Kendall's tau\_b rank correlation coefficients. The unique contribution of network and financial strain to outcome group was examined in a stepwise linear regression analysis.

Statistical significance was set at  $p < 0.05$  (two-tailed) in all tests.



## RESULTS

The results in all papers refer to the study population included in the Parachute Project. Study I also includes the historical and prospective comparison groups and study V includes persons from the PART-study. Differences in numbers and proportion are explained by differences in the number of patients at each follow-up time and by missing data in some variables, see Table 2.

### STUDY I

Only patients with schizophrenia syndromes (i.e. schizophrenia, schizophreniform and schizoaffective disorder) were included in this study to make the groups more homogenous. The 61 consecutive first episode schizophrenia syndrome patients were followed over three years. They were compared with the 25 FEP patients from the Prospective group from a high quality social and biological psychiatry centre where all patients were treated in inpatient care and 41 FEP patients from a historical “treatment as usual” group from three clinics in the Stockholm area. In some of the comparisons there were only data available in the Prospective group. The results showed that there were no differences between the groups regarding, symptom load and working capacity at year three but there was a difference compared to the Historical group regarding level of functioning, the parachute group had higher scores on GAF. The percentage of patients treated with antipsychotic medication and prescribed doses at 36 months did not differ between the groups. Almost all patients in the three groups had been treated with antipsychotic medication, at least during some period. Antidepressants and Lithium (and similar medications) were prescribed to similar extent during the year three in the groups. More patients in the Historical group were on depot medication. The proportion of patients on disability allowance and sick leave >12 months during the third year did not differ to the Prospective group (38% of parachute vs. 36% of Prospective) but was lower than in the Historical group (59%). The main difference between the Parachute Project and the Prospective group was the treatment costs. In spite of the increased outpatient care involvement together with the considerably low number of inpatient days in the parachute group the mean direct costs were about half of those in the Prospective group during the first year.

### STUDY II

The aim of this study was to evaluate the impact of factors presented before or at the patients’ first admission to psychiatric care on the patients’ satisfaction with care (PSC) one year after entering the Parachute Project. One hundred and thirty-four out of 175 FEP patients completed a patient satisfaction questionnaire. The non-participants were younger, had fewer days at work the year prior to first admission and fewer of them had a social network capable of cooperation. The associations between demographic and psychosocial background factors together with psychiatric and functional status before and at admission to the PSC were analyzed. The result showed that 29 % of the variance of PSC was explained by factors such as educational level, social network, DUP and GAF the year prior to onset. Negative symptoms and lack of hope at admission were also predictors of a lower satisfaction with care. The strongest predictor was DUP; longer DUP was related to lower PSQ.

### STUDY III

The aim of this study was to construct a long-term prognostic rating scale on the basis of clinical characteristics in FEP patients. Baseline characteristics, DUP, family history of psychosis, premorbid characteristics and cognitive functioning were put in relation to five-year outcome in 153 FEP patients. Eighty-five patients (37 males, 48 females) showed a good outcome and 68 patients (44 males, 24 females) showed a poor outcome measured with the dichotomized comprehensive outcome measure.





Because of a non-congruent high dropout rate for the cognitive variables, they were not included in the logistic regression analysis. Differences in performance and verbal IQ between the two outcome groups were compared in a two-way repeated analysis of variance (groups\*tests). Patients with a poor outcome exhibited worse performance (verbal IQ:  $78.4 \pm 15.40$  and performance IQ:  $86.1 \pm 14.73$ ) than those with a better outcome (verbal IQ:  $87.2 \pm 16.52$  and performance IQ:  $94.1 \pm 18.34$ ). Sixty-three percent of those with a diagnosis of schizophrenia syndrome had a poor outcome, which can be compared with 35% of those with another type of psychosis. The relative contribution of the baseline characteristics to the 5-year outcome was analyzed and five variables were found to have unique contributions in the prediction of outcome. In order of magnitude of the odds ratios these variables were “the highest GAF the year before first admission  $\leq 70$ ”, “the highest educational level is compulsory school”, “GAF at first admission  $\leq 30$ ”, “male gender” and “contact with friends  $\leq 2-3$  times/month”. Eighty-one percent of the patients were correctly classified by the regression equation (cut-off score = 0.50). The sensitivity, i.e. correctly identified cases (poor outcome), was 0.84 and the specificity 0.77, i.e. the correctly identified non-cases (good outcome). The result showed that a scale based on premorbid characteristics may be useful in a clinical context when developing an adequate treatment plan for patients at risk of a poor outcome and with first-episode psychosis.

#### STUDY IV

This study aimed to examine gender differences in the prediction of five-year outcome in FEP patients. Eighty-one male and 72 female FEP patients were compared regarding the sensitivity and specificity of the Predictive Rating Scale (PRS) and the result showed that the sensitivity was higher among males (males 71% and females 36%). Due to this, gender specific predictors of five-year outcome were examined. The results revealed that previously described predictors differed between genders. Significant gender differences were shown regarding the relation to five-year outcome in the following baseline variables: symptom tension at baseline, age  $\leq 25$  years at first admission, highest educational level is only compulsory school, and lives with parents. In a next step the unique contribution of the baseline variables to five-year outcome (symptoms not included) was examined according to gender. This showed that among males only two of the variables had a unique contribution: “the highest GAF the year before admission” and “the current GAF at first admission”. In females the corresponding variables with unique contribution to five-year outcome were “the highest education being compulsory school”, “living with parents” and “contact with friends  $\leq 2-3$  times a month”. In order to increase the sensitivity of the PRS among females the presence of the risk-factor “just compulsory school” was given two points instead of one for females and this increased the sensitivity to 59 %, in the females having a sum of  $\geq 3$  risk factors and having a poor outcome, compared to 71% of the males. The results show that the PRS feasibility can increase when gender differences in the risk factors are taken into account. Additionally the study showed that females with “the highest education being compulsory school” performed significantly worse in the WAIS-R Full Scale IQ ( $p < .01$ ), Verbal IQ ( $p < .01$ ) and Performance IQ (NS) than those with higher education. Among males there were no such differences.

#### STUDY V

The aim of this cross sectional study was to examine the impact of perceived financial strain and quantitative and qualitative network to level of recovery in FEP and in healthy controls. In year 2001, five to six years after admission, 133 out of the remaining 135 patients in the Parachute Project received a questionnaire from the PART study, a population-based study of mental ill health in Stockholm County. The PART questionnaire included questions about qualitative and quantitative network as well as experience of financial strain. Sufficient data were obtained from 53.3% (71 persons). To each FEP person (52 recovered 19 non-recovered) four persons ( $n=284$ ) from the second wave in the





PART study were matched according to age and gender. Persons with a diagnosis of psychosis in the inpatient register and those stating that they had had a psychiatric disorder or were on psychotropic drugs were excluded. The relation between qualitative and quantitative network and experience of financial strain to outcome group (PART people, recovered FEP patients and non-recovered FEP patients) was examined. The results showed that financial strain, quantitative social-network and qualitative social-network all had unique contributions to outcome group. The variables entered the regression model in the following order: quantitative social-network ( $\text{Beta}_{\text{stand}} -0.19$  ( $p=0.002$ )), financial strain ( $\text{Beta}_{\text{stand}} 0.17$  ( $p=0.001$ )) and qualitative social-network ( $\text{Beta}_{\text{stand}} -0.18$  ( $p=0.003$ )). The regression model accounted for 16% of the variance in the outcome group (Adjusted  $R_2$  0.16), which implies that financial strain and quantitative social-network and qualitative social-network together explained 16% of the variance in the outcome groups.





## DISCUSSION

The overall aim of the present thesis was to extend knowledge about outcome in FEP patients. Outcome can be measured in many ways and many outcome measures give only a part of the picture of the outcome in a person's whole life. The evidence of the advantages of integrated care models has both increased in number and in strength. We hope that more comprehensive models will also gain ground in psychotic disease classification and in outcome assessment.

### THE NEED-ADAPTED TREATMENT MODEL

The results from the Parachute Project show that it is possible to create and implement a large scale system of care that values a high degree of psychosocial support, lowest optimal antipsychotic medication, participation of families and treatment in normalized, humane and comprehensive settings (110, 118) with continuity over five years. At 12 and 36 month follow-up, data indicated that outcome in this new system of care was at least comparable with usual treatment (110, 118). Two RCTs of integrated treatment for FEP patients, The OPUS study and the LEO-study, have later confirmed this conclusion (119). However, there is still a lack of long-term follow-up studies that can further confirm our results. Additional research is needed to study which of the principles behind the Parachute Project that was most important. The study was a comparison of an integrated need-adapted treatment concept in naturalistic design and not of different specific treatment methods. The low rate of inpatient admissions during years two and three, in combination with a low degree of symptoms, and low suicide rate, indicates that the need-adapted policy worked satisfactorily. Social recovery was good and the high level of satisfaction with care makes it more likely that the patients will be open to further contact when, and if, necessary,

### COST AND CLINICAL OUTCOME

To our knowledge, there are no previous studies regarding cost effectiveness in the care of FEP patients. Our findings showed that the mean direct costs per patient with a schizophrenia spectrum diagnosis in the Parachute Project were about half of those in the Prospective group (118), in spite of the increased outpatient care involvement. This was related to the considerably lower number of in-patient days, The Parachute patients were mainly treated in outpatient service according to the policy. Our study thus showed that it is possible to focus on outpatient care and alternative forms of inpatient care to a larger extent without increasing the costs and without worsening the results. It also showed that the amount of inpatient treatment was most important when calculating the costs.

### PATIENTS' SATISFACTION WITH CARE

The satisfaction with care in the Parachute Project was high among both patients and families (110, 116). Since a frequent finding in the literature is that most people say they are satisfied with the care they have received (120, 121) we wanted to examine the impact of pre-onset and baseline variables on the PSC. Of the examined variables, the strongest unique predictor was DUP. Longer DUP pre-admission was related to lower scores of PSC. The presence of psychotic symptoms might have affected the patients' pre-conception in a negative way. Loss of health affects the patients' "health beliefs" leading to less confidence/trust in their own power and an increased sense of dependence on powerful others. This has been shown to be related to prolonged DUP (122). It was somewhat unexpected that a low GAF score the year before onset was related to higher PSC. The period of low GAF before the psychotic symptoms started consisted probably in a combination of declined function level together with various degrees of prodromal symptoms, such as anxiety and depression. Before the psychotic symptoms started the patients' insight in the developing problem was not muddled by the psychosis itself. Patients with a lower pre-psychotic GAF score in combination with shorter DUP might have





felt a need for help from professionals, thus they became satisfied when they received psychiatric care. The results indicate the importance of early intervention to shorten the DUP period. By reaching the public with relevant information it may be possible to detect signs of the development of psychosis even earlier; thus enabling earlier intervention. Additionally, interventions to decrease negative pre-conceptions about psychiatric problems and psychiatric healthcare by increasing knowledge in the lay public will hopefully both decrease prejudice and increase confidence in the psychiatric care system. The TIPS project in Norway has good experience of using intense information strategies using all available media in combination with specialized detection teams to reach young people in order to decrease DUP (89). However, in a review Read et al, (123) found that biogenetic beliefs and diagnostic labelling regarding schizophrenia were associated with perceptions of dangerousness, unpredictability, prejudice, fear and desire to keep them away from the public. Modern society's tendency of placing much of the responsibility for one's own life on the individual person will probably increase self-blame and self-stigmatization (124). This raises the question of how to impart information about psychotic states in order to decrease ignorance and prejudice without producing counterproductive effects in the form of increased prejudice. There is still a lack of knowledge about how our pre-conceptions affect our approach to psychiatric problems and psychiatry and this needs to be focused on more in future research.

## **PREDICTION OF OUTCOME**

Psychosis and schizophrenia are heterogeneous conditions and the diagnostic groups include patients with different psychotic features and different outcomes. Schizophrenia may be a syndrome comprising several disease entities, which can be deconstructed into several pathologic domains with more than one latent structure (6). Understanding the factors that predict outcome in first-episode psychosis can lead to the development of strategies for prevention and treatment. There is evidence that a shortened DUP improves prognosis (55). In addition to DUP-reducing strategies, early identification and treatment planning for patients at risk of a poor long-term outcome may be necessary to improve long-term outcome (44, 50, 125). The importance of an early identification of those among first-episode psychoses at the risk of a poor long-term outcome is crucial when the social network, such as family and friends, is still available for cooperation (108). A decline in cognitive functioning typically occurs in the early phase of a psychosis, especially in schizophrenia. If cognitive functions are not restored during the remission period after the first acute phase of illness, the patient's social functions may be insufficient with a poor outcome as a consequence (72, 73). In the Parachute Project, Carlsson et al. (71) have shown that cognitive function at baseline predicts both 1,- and 3-year outcome. Neuropsychological testing may therefore be a useful tool to identify those at risk of a poor outcome in the early phase of illness. However, patients at first admission with psychotic symptoms can hardly be subject to extensive neuropsychological testing, and further, the ordinary psychiatric staff can rarely perform such tests. The PRS offers an alternative that is easy to use, requires a minimum of training and can be easily applied at first admittance. A person with a score of four or five risk items may benefit from maintaining contact with the ACT-team in order to prevent social decline. Identifying patients at risk for poor outcome requires a treatment approach with hopefulness and a constructive attitude thus minimizing the risk of producing iatrogenous effects such as hopelessness and stigmatization. The identification of risk for poor outcome aims to provide a basis for steering the efforts of help and support towards where they most are needed and not to point out "hopeless cases".

## **GENDER DIFFERENCES IN THE PREDICTION OF OUTCOME**

Since there are gender differences in the onset and course of schizophrenia there may also be differences in prediction of outcome. Among the variables included in the PRS the "educational"





item was the best predictor of a poor outcome for females whereas the best predictor for men was a low preadmission level of functioning (the highest GAF the year before first admission  $\leq 70$ ). It was remarkable that while females with “only compulsory school” performed worse in cognitive tests than females with more education, there were no such differences in males. Can low education be a selection variable in females identifying those with pre-morbid cognitive disturbances and at risk for poor outcome? In Sweden there exists no gender bias in entering secondary-upper school; males and females continue with studies to the same extent after compulsory school. The expectation is that nearly all young males and females continue to study. Weiser et al. found that healthy female adolescents, who in the future will develop schizophrenia, had poorer performances in pre-morbid cognitive testing than males (126). This may indicate that male and female adolescents have different reasons for not continuing studying. These results raise many questions and further research is needed. However, after the adaptation of the PRS (the education item give 2 points in females) for females with poor outcome the proportion of having  $\geq 3$  items increased from 8 to 13 which meant that the sensitivity increased from 36% to 59% and that the specificity decreased from 96% to 85% which furthermore stresses the need of gender specific research.

### **FURTHER DEVELOPING THE PRS**

The results of the PRS studies need to be confirmed by examining other FEP populations. The high sensitivity and specificity in the regression analysis model were dependent on the weightings (OR) of the items entered in the model and this has to be taken into account in the continuing development of the PRS to increase its sensitivity and specificity. Unfortunately there is no clinical screening of cognitive impairment available that can be performed by ordinary staff at the patient’s first contact with psychiatric care, which could further strengthen the predictive potential of the scale. Hofer et al. (127) have, for example, shown that the Positive and Negative Symptom Scale is a poor proxy for cognitive functioning measured with a neuropsychological test battery. However, there is promising current work in developing brief cognitive screen instruments which might change this (128, 129). At present the neuropsychological test battery has to be complemented afterwards and cannot be replaced by any short-cut proxy that can be included in the PRS. When the patient’s condition allows the neuropsychological test battery to be performed it is a necessary complement to the PRS and can provide additional information about the patient’s strengths and weaknesses, which can serve as a basis for further treatment planning. Furthermore, possible advantages of developing gender specific assessment tools must also be considered. A validation study of the PRS is in progress in co-operation with the EPPIC research group in Australia.

### **NETWORK AND FINANCIAL STRAIN**

Financial strain, quantitative social-network and qualitative social-network all made unique contributions to the outcome group. However, without knowing the causal association it is not possible to conclude that financial strain will impede socialization after a psychotic break down or vice versa, if poor network is a mediator of financial strain. A cross-sectional study like this results in a cause-effect confusion. It is well known that financial strain, i.e. due to unemployment, affects both somatic and psychiatric health negatively (7). In psychiatric practice there might be a risk that clinicians’ pre-conceptions lead to the conclusion that lack of social network among people suffering from psychosis is only due to the psychotic disorder per se. Interventions to improve and hinder loss of network might then be based on the wrong conclusions. Focusing solely on the disease might make us blind to environmental interactive factors that might affect the course of the illness. “Normal” stressors such as financial strain might affect the person suffering from psychosis as much as, or more, than healthy people. FEP patients might benefit from interventions that reduce their financial strain thus facilitating daily life and participation in cultural and social activities during the process





of recovery. The study showed that the poorer the psychiatric health, the poorer the self-reported network and financial situation. Social and financial strain need to be addressed more in psychiatric research and interventions.

## **METHODOLOGICAL ISSUES**

There are some methodological considerations that need to be highlighted and discussed in the interpretation of the findings in this thesis. First some overall issues relevant for all the included studies followed by some study specific considerations.

### **General considerations**

#### *Research design*

Randomized controlled trials are the gold standard of efficacy studies. RCT:s give reliable results that can be generalized and repeated under standardized conditions. However, generalisability might not always be valid. Good efficacy of an intervention within the controlled study design can show less effectiveness in real life. Pragmatic research and outcomes focus on whether an intervention works under real life conditions and whether it works in terms that matter to the patient. Strengths of observational studies mirror the weakness of RCT (29). The research in this thesis was based on efforts to improve everyday clinical practice. It was not possible to randomize the patients, some of the participating clinics had too few patients and furthermore they could not provide two separate treatment regimes, one need-adapted and one with standard treatment. Randomizing to effective treatment versus no-treatment is ethically impossible in this group of patients. However, the overall methodological considerations in the Parachute Project are the lack of randomized control groups and the limitation of the comparison groups. The limitations in the Historical group are the “time-bias,” i.e. the collection of data in the Historical group was performed five years earlier than in the Parachute group. Thus differences between the Historical group and the Parachute group can be due to differences in society and care policy due to time-bias. Furthermore the, data were mainly collected from hospital records and available databases. The prospective comparison group was running at the same time as the Parachute Project but the possibility that the county where it was situated had some systematic differences, compared to the centres included in the Parachute Project cannot be excluded. Furthermore, the treatment in the prospective comparison group changed over time and became more and more integrated, with increasing focus on outpatient care. Unfortunately, due to financial reasons, the ordinary staff performed both treatment and assessments in the Parachute Project as well as in the Prospective comparison group. Such a research design means a logistic challenge and a huge workload for the staff. This was the reason that the Prospective group could not obtain data at the five-year follow-up; thus data was only available in the Historical group.

#### *Participants*

It is well known that persons experiencing psychosis tend to decline participation or decide to stop participating prematurely. The response rate can often be <50%. It is also probable that those who become non-participants differ from those who participate leading to loss of information, which might bias the results. In the Parachute Project the remaining participants over five years were 77% (135), which can be considered satisfactory. Additionally, it was possible to obtain comprehensive outcome measure from 87 % (153) of the patients.



## Study specific considerations

### *Study I*

In this study only patients with a schizophrenia syndrome diagnosis were included in order to make the groups more homogenous. This was based on doubts whether the Prospective group captured all non-schizophrenic psychosis and thus the non-schizophrenic patients were excluded. This limits the possibility to generalize the results to all psychoses and the lack of comparison studies on long-term outcome of non-schizophrenic psychosis remains unchanged. Also, the statistical power was lowered. The difficulties in obtaining an exact cost of the crises homes forced us to set the same price for all of these accommodation units as for the hospital wards probably leading to a higher cost. However, doing so protected us from biased results. On the other hand, we have not been able to actually calculate the increased indirect costs, which tend to follow more intense outpatient work, i.e. supervision, training, conferences, home visits, etc. Also, we have not calculated the social costs involved in having a sick pension or not being able to work. The figures regarding pension and working ability are, however, very similar in the Parachute and the Prospective groups. Furthermore, the skewed distribution of inpatients after the first year (one Parachute patient occupying inpatient resources for the whole 2<sup>nd</sup> and 3<sup>rd</sup> year) reduced the possibilities of detecting significant differences between the groups during years 2 and 3.

### *Study II*

The main limitation of this study was the use of a new not validated questionnaire and the lack of comparison group data. The PSC was developed specifically for the need-adapted treatment for FEP patients and was not possible to use in the “treatment-as-usual” Prospective group. It is possible that the aim of the study, to examine determinants of patient’s satisfaction, could have been fulfilled with a general patient satisfaction questionnaire. This could have been feasible for both the Parachute group and the Prospective group thus creating the opportunity to examine if PSC and determinants of PSC differ between groups.

### *Study III*

The most important limitation of this study was that the transformation of the  $\beta$ -weights of the significant risk factors generated in the logistic regression analysis to the PRS were given the same weight for all risk factors (one risk factor = one point). This reduced the sensitivity and specificity of the scale. To develop an easily handled and appropriate tool for assessment of risk factors for unfavourable outcome is a balance between making it as exact as possible but still maintaining its appropriateness and ease of administration. Another limitation was, due to the high rate of non-responders, that the neuropsychological test results were not included in the regression analysis thus precluding the possibility of examining the impact of cognitive function in relation to the other predictors.

### *Study IV*

The core limitation of this study was the low power not allowing to statistically secure the results i.e. adjustments for multiple comparisons. In addition, this study had the same limitations as Study III due to their connection and this limited the methods used when examining gender specific predictors.

### *Study V*

The main limitation of this study was the cross sectional design that made it impossible to study examine variable interdependency. Thus causation can only be discussed in the light of previous



results from other studies and common sense regarding reasonable interaction. Another limitation is the number of non-participants, which weakens the possibility to generalize the results.

## **OVERALL CONCLUSION**

This thesis examines different aspects of outcome in FEP patients and some general conclusions can be made. Firstly, it is possible to provide need-adapted care to persons suffering from severe mental illnesses such as psychosis and schizophrenia. However, more studies with naturalistic design are needed to increase knowledge about what ingredients are effective and how various interventions work together. Effectiveness in psychiatric care has to be studied in “real life”. Secondly, outcome studies in FEP have to consider and adapt a holistic view. Also, it is not sufficient to measure outcome with only symptom level or to overlook important aspects such as gender and age. Furthermore, diagnosis is neither an optimal predictor nor an optimal outcome measure. Patients have to be divided into other subgroups/classes based on categories and dimensions such as age, gender, childhood, school-performance, functioning and symptoms, in order to avoid the risk of making inadequate comparisons. Both the independent variables as well as the dependent variables have to cover as many different aspect of life as possible. The psychiatric services have to adopt a holistic view and not only consider the psychotic symptoms as their area of interest and responsibility. Helping young people that experience psychosis includes focusing on issues related to their whole life and society. The research must benefit the patients, i.e. if an RCT shows efficacy for a specific intervention the importance might be lost if the effectiveness in “real life psychiatric practice” is not considered.

The gap between what we know is best (research results and empirical knowledge) and what we really do (clinical reality) must be focused on in order to close the gap between the theoretical level, the good clinical examples and the everyday practice. How to implement evidence-based knowledge is a question of its own also requiring research.

## **ETHICAL CONSIDERATIONS**

The Ethical committee of the Karolinska Institute (dnr. 95–399) approved the Parachute Project. However, research in FEP might present greater challenges than those encountered in other research. Patients are asked to participate in the research at the same time as they are experiencing their first psychotic crisis. Symptoms may include fear, suspiciousness, and delusions, which may further complicate matters. Studies involving FEP patients’ needs take into account all persons involved.

## **FURTHER STUDIES**

The promising results from integrative need-adapted treatment programmes have to be confirmed in further studies. The impact of the specific ingredients in the programmes has to be examined. Prediction of outcome has to be continuously developed. A validation study of the PRS is in progress. The role of gender in psychiatric health should be illuminated and all results in psychiatric research should be presented by gender. Furthermore, conditions that primarily are not psychiatric but significantly can affect psychiatric health, such as socio-economic deprivation and inequalities should be focused on by the research community.





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